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# Systemic immune correlates of long-term survival after Delta-24-RGD based on the Therapeutic Adenovirus for Recurrent Glioblastoma Effect Trial (TARGET)

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## Abstract

**Purpose:** To evaluate the combination of intra-tumoral Delta-24-RGD and subcutaneous interferon gamma (IFN-g) in patients with high grade glioma (HGG), based on the rationale that augmenting the immune response with IFN-g will increase the efficacy of Delta-24-RGD treatment.

**Patients and methods:** In this Phase 1b, multicenter, randomized trial (NCT02197169), we evaluated the combination of intratumorally injected Delta-24-RGD with subcutaneously administered Interferon-gamma (IFN- $\gamma$ ), a potent activator of T-helper 1 CD8+ cell immune response, in 37 patients with recurrent HGG, and investigated systemic immune correlates of long-term survival. Twenty-seven patients were randomized 2:1 into two cohorts: Delta-24-RGD (via standard biopsy needle) with IFN- $\gamma$  or Delta-24-RGD alone (via standard biopsy needle). In an expansion cohort, 10 patients received intra-tumorally injected Delta-24-RGD via the MEMS Cannula.

**Results:** Although the addition of IFN- $\gamma$  to Delta-24-RGD did not significantly increase the percentage of long term survivors compared with Delta-24-RGD alone, the IFN- $\gamma$  cohort had the longest-surviving patients (OS 44.2, 23.7, 20.6 and 20.1 months). Post-hoc analysis of plasma and peripheral blood mononuclear cells using Viral Phage Immunoprecipitation Sequencing Antibody Reactome profiling of viral epitopes (VirScan) and single cell RNA sequencing (scRNA seq) revealed that levels of circulating anti-adenovirus specific IgG and CD8+ NKT-like cells 2 months after treatment with Delta-24-RGD distinguished long-term survivors from short-term survivors.

**Conclusions:** Immunological fitness, assessed by an anti-adenoviral specific antibody response and higher levels of activated CD8+ NKT-like cells after Delta-24-RGD treatment, may have utility as an early surrogate of a robust systemic immune response that correlates with long-term survival.

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